REMARKS

New Claims

Prior Claims 1-66 have been cancelled and new Claims 67-124 are newly presented here. New Claims 67-124 correspond largely to the prior Claims 1-66, except that the claims have been reorganized so that dependent claims directly follow the independent claim from which they depend. For the Examiner's convenience, the following table summarizes the support for the new claims with reference to the previously presented, now cancelled, claims. In addition, although it is not expressly permitted by 37 CFR 1.121(c), claims that are new, but correspond to currently withdrawn claims (according to the species election in this application) have been denoted as "Withdrawn-New". This terminology is considered to be an acceptable alternative to "Withdrawn" as of June 6, 2005 (see USPTO website), and has been used here to facilitate the Examiner's comparison of the prior claims with the new claims. Support for particular aspects of some new claims is provided in the discussion of rejections below.

New Claim	Prior Claim/Support	New Claim	Prior Claim/Support
67	1	96	44
68	6	97	47
69	7	98	48
70	38	99	49
71	8	100	50
72	9	101	51
73	10	102	52
74	12	103	53
75	14	104	26
76	39	105	42
77	37	106	15
78	24	107	17
79	25	108	18
80	28	109	19

81	29	110	20
82	30	111	21
83	31	112	40
84	43	113	57
85	32	114	Example 1, 4
86	33	115	58
87	34	116	16
88	35	117	Example 1, 4
89	36	118	22
90	2	119	54
91	45	120	55
92	Example 1, 4	121	56
93	3	122	41
94	5	123	60
95	46		

Claim Objections

The Examiner has objected to Claims 16, 25, 41 and 53 (now Claims 116, 79, 122, and 103, respectively) for reading on non-elected species. Applicants note the Examiner's objection to these claims, and submit that the issue will be resolved as necessary when all other issues in the application have been resolved.

Rejection of Claims 1, 2, 24, 26, 38, 43, 44 and 52 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claims 1, 2, 24, 26, 38, 43, 44 and 52 under 35 U.S.C. § 112, second paragraph, contending that these claims are indefinite.

First, the Examiner contends that it is unclear in Claims 1 and 2 whether the fusion protein may contain a variable region or whether it applies only to the Ig domain.

In reply, Applicants note that Claims 1 and 2 (now Claims 67 and 90), respectively)

recite two components for the fusion protein: (1) a soluble protein selected from a growth factor, a cytokine that is not interleukin-10, and an active variant of the growth factor or cytokine; and (2) an immunoglobulin (Ig) domain that does not contain a variable region. It is submitted that the term "variable region" is an art-accepted term that refers to a particular domain of an *immunoglobulin* molecule (*e.g.*, see page 1, lines 21-30). Therefore, given that the immunoglobulin domain may not contain a variable region, and given that the other component in the fusion protein is a growth factor or cytokine, neither of which comprises a "variable region", then it seems clear that neither the immunoglobulin domain nor the fusion protein of which it is a part contain a variable region. Claims 67 and 90 have been restructured with regard to the position of this phrase to try to clarify the language for the Examiner.

The Examiner also contends that the phrase "the cytokine is not IL-10 or an interferon" in Claim 2 is unclear.

Claim 2 (now Claim 90) has been rewritten to clarify that neither IL-10 or an interferon are included in the reference to a cytokine.

The Examiner contends that Claims 38 and 44 are indefinite because depending on what assay is used, the EC_{50} will vary.

Claims 38 and 44 (now Claims 70 and 96, respectively) have been rewritten to recite that the EC_{50} is determined using a cell line that proliferates in response to EPO. Similar amendments were made to withdrawn Claims 9 and 48 (now Claims 72 and 98, respectively). Support for these amendments is found in Example 3.

The Examiner contends that Claims 24 and 52 are not further limiting as the claims are to a protein and not to a composition.

Claims 24, 25, 52 and 53 (now Claims 78, 79, 102 and 103, respectively) have been rewritten to recite a composition instead of a protein.

The Examiner contends that Claims 26 and 43 are incomplete for omitting the following essential steps: the expression vector is missing and the method of protein expression in the cells is not mentioned.

Claims 26 and 43 (now Claims 104 and 84, respectively) have been amended to provide the steps noted by the Examiner.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 2, 24, 26, 38, 43, 44 and 52 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1, 6, 7, 24, 25, 28-31, 37 and 43 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claims 1, 6, 7, 24, 25, 28-31, 37 and 43 under 35 U.S.C. § 102(b), contending that these claims are anticipated by Sytkowski et al. (WO 99/02709). Specifically, the Examiner contends that WO 99/02709 teach the construction and production of EPO-Ig fusion proteins. The Examiner asserts that WO 99/02709 teach an EPO protein that is fused at its N- or C- terminus to an Ig constant domain or region. The Examiner contends that WO 99/02709 teach that the EPO can be fused to the Ig domain directly or via a linker of between about 1 and 20 amino acids. The Examiner also contends that WO 99/02709 teach that the EPO-Ig fusions can be dimers if two monomers are joined.

Applicants traverse the Examiner's rejection under 35 U.S.C. § 102(b). Initially, it is noted that the present invention claims priority to July 13, 1999, and therefore, WO 99/02709 is only available as prior art under 35 U.S.C. § 102(a). Applicants submit that WO 99/02709 does not teach or suggest the present invention as claimed.

First, Claim 1 (now Claim 67) and its dependents are directed to direct fusions between the recited proteins and an Ig domain (*i.e.,* fusions without an intervening peptide linker). With regard to the direct fusion of EPO to an IgG domain, Applicants refer the Examiner to the attached Declaration under 37 CFR 1.132 of Dr. George Cox, a coinventor of the present invention. The Declaration of Dr. Cox provides a discussion that although Sytkowski et al. *postulates* that one could make a direct fusion between EPO and IgG-Fc, the publication is non-enabling for this fusion. Specifically, as discussed in the Declaration, Sytkowski et al. clearly did not fully appreciate the structure of a direct fusion of EPO and IgG-Fc domains because it is impossible to use the method taught in Sytkowski et al. to

construct such a protein. To attempt to use the method described by Sytkowski et al., one would have to either insert a linker or change the amino acid sequences at the joined ends of the protein (which results in the creation of a linker and further modifies the joined proteins). No other method is described in WO 99/02709 for the production of an EPO-IgG fusion protein, and this publication provides no working examples of a direct fusion between EPO and an Ig domain, or indeed, of any actual EPO-IgG domain fusion (note that all of the Examples in Sytkowski et al. are prophetic). Therefore, Applicants submit that Sytkowski et al. (WO 99/02709) does not actually teach an EPO-IgG fusion protein as claimed in Claim 67 (formerly Claim 1) as asserted by the Examiner because the publication is non-enabling for the production of such a protein. Therefore, Sytkowski et al. fails to anticipate Claim 67. Accordingly, Applicants submit that none of Claims 6, 7, 24, 25, 28-31, 37 and 43 (now Claims 68, 69, 78,-83, 77 and 84, respectively) are anticipated, as these claims all depend from Claim 67.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 6, 7, 24, 25, 28-31, 37 and 43 under 35 U.S.C. § 102(b).

Rejection of Claims 15, 16, 19, 20, 40 and 57 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claims 15, 16, 19, 20, 40 and 57 under 35 U.S.C. § 102(b), contending that these claims are anticipated by Sytkowski (U.S. Patent No. 6,242,570). Specifically, the Examiner contends that the '570 patent teaches a multimeric fusion protein comprising two or more members of erythropoietin joined with or without a peptide linker. The Examiner asserts that the '570 patent gives a list of GH supergene family members[sic] and teaches that the linker may include serine, glycine and asparagine, or threonine and alanine, and that the length may vary without significantly affecting the biological activity of the fusion protein.

Applicants traverse the rejection of Claims 15, 16, 19, 20, 40 and 57 (now Claims 106, 116, 109, 110, 112, and 113, respectively) under 35 U.S.C. § 102(b). With regard to Claims 106, 109, and 110, it is noted that these claims recite a homomultimeric protein

joined without an intervening peptide linker, and Claims 116, 112 and 113 recite a homomultimeric protein joined with a peptide linker that has been limited to a linker of between 2 and 7 amino acids and consisting of only glycine or serine.

Initially, with regard to 106, 109 or 110, or any dependent claims therefrom, as in the other Sytkowski et al. reference discussed above (WO 99/02709), while a direct fusion (no intervening linker) of EPO to EPO is *hypothecated* (column 3, line 32), no actual example of how to construct the EPO dimers without a linker are provided. Moreover, the '570 patent provides absolutely no teaching or guidance whatsoever with regard to how to make a direct fusion between EPO monomers. As discussed above, the same author (Sytkowski), in attempting to teach a direct fusion of EPO to another protein in the WO 99/02709 publication discussed above, taught a method that was *inoperable* for the production of a direct fusion as taught and claimed in the present application. Therefore, as with WO 99/02709, Applicants submit that the '570 patent is non-enabling for the teaching of a direct fusion of EPO to other EPO proteins. Furthermore, Applicants submit that the WO 99/02709 publication demonstrates that one can not assume that the ability to produce such a direct fusion was within the ability of those of skill in the art and particularly, that this was not within the ability of Sytkowski (noting that WO 99/02709 and the '570 patent are contemporaneous with regard to filing dates). The only multimeric fusion protein actually exemplified in the '570 patent is an EPO-EPO dimer, which is joined by a peptide linker of 17 amino acids. In addition, the linker is joined to the second EPO protein by a BamHI restriction site. As discussed by Dr. Cox, it is not possible to create a direct fusion between EPO monomers this way because the Bam HI site will always result in the creation of extra amino acids other than the EPO amino acids, which form a peptide linker (*i.e.*, the only method taught by the '570 patent to join EPO monomers will always use a peptide linker). Therefore, one can not use any of the specific teachings of the '570 patent to construct a direct fusion between EPO monomers. Accordingly, Applicants submit that one of skill in the art is not actually taught by the '570 patent how to make or use a homomultimeric EPO direct fusion protein as presently claimed (nor any homomultimeric direct fusion protein as

claimed), and as such, the '570 patent does not anticipate Claims 106, 109 or 110, or any dependent claims therefrom.

With regard to teachings regarding EPO-EPO proteins comprising a linker, in column 4, beginning on lines 33, the '570 patent states that the linker length should be of sufficient length to allow the two proteins to fold properly (this also provides an additional teaching away from making a direct fusion between EPO monomers). Later, in column 4, beginning on line 59, the author states that the linker length may vary, but the only guidance provided with regard to the actual linker length is that the EPO proteins should be separated by a linker length of 10-20 amino acids, although *longer* linker sequences may be used, with a preferred linker length of about 15 amino acids. Therefore, the '570 patent clearly teaches that the linker should be at least 10 amino acids in length, and preferably longer. Moreover, as discussed above, the only multimeric fusion protein actually exemplified in the '570 patent is an EPO-EPO dimer, joined by a peptide linker of 17 amino acids. The linker contains alanine, glycine, serine and threonine amino acids. In contrast, the present claims recite that the linker is between 2 and 7 amino acids, which is well outside of the teachings of the '570 patent. Indeed, the '570 patent appears to *teach away* from the use of such small linkers. Therefore, the '570 patent does not anticipate Claims 116, 112 and 113 or any dependent claims therefrom.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 15, 16, 19, 20, 40 and 57 under 35 U.S.C. § 102(b).

Rejection of Claim 41 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claim 41 under 35 U.S.C. § 102(b), contending that this claim is anticipated by Amoresano et al. Specifically, the Examiner contends that Amoresano et al. teach human GM-CSF/EPO fusion protein and the linker comprising glycine, serine and alanine residues. The Examiner contends that Amoresano et al. teaches an eight amino acid peptide sequence comprising glycine, serine and alanine.

Applicants traverse the rejection of Claim 41 (now Claim 122) under 35 U.S.C. §

102(b). Claim 122 recites a multimeric fusion protein comprising two or more different members of the Growth Hormone supergene family joined by at least one peptide linker that consists of a mixture of between 2 and 7 amino acid residues selected from glycine and serine. Amoresano teach an eight amino acid sequence comprising glycine, serine and alanine, and therefore, Amoresano does not anticipate the presently claimed invention.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claim 41 under 35 U.S.C. § 102(b).

Rejection of Claims 2, 26, 42, 45, 46, 52, 53, and 62-65 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 2, 26, 42, 45, 46, 52, 53, and 62-65 under 35 U.S.C. § 103, contending that these claims are unpatentable over Sytkowski et al. (WO 99/02709) in view of Curtis et al. Specifically, the Examiner contends that Sytkowski et al. teach the construction and expression of the EPO-Ig fusion protein including the use of a linker to join two proteins. The Examiner admits that Sytkowski et al. do not explicitly discuss the peptide linkers that can join a fusion protein. However, the Examiner asserts that Curtis et al. teaches a multimeric fusion protein comprising two or more members of the GH supergene family joined with or without a peptide linker, and that the length of the linker may vary from 1-500 amino acids or preferably from 1-20 amino acids and can include serine and glycine. Therefore, the Examiner contends that it would have been obvious to combine the references to use different forms of the peptide linkers taught in Curtis et al. in the fusion protein of Sytkowski et al. The Examiner further contends that one of ordinary skill in the art would have been motivated to modify the teachings of Sytkowski et al. because it is routine in the art to determine linker lengths.

Applicants traverse the rejection of Claims 2, 26, 42, 45, 46, 52, 53, (now Claims 90, 104, 105, 91, 95, 102 and 103, respectively) and 62-65 under 35 U.S.C. § 103. It is noted that the subject matter of prior Claims 63-64 has been cancelled and the subject matter of prior Claim 65 has been moved into new Claim 90. Initially, with regard to WO 99/02709, as the Examiner admits, this publication does not teach the amino acid sequences or DNA

sequences of any peptide linkers. Curtis et al. teaches a heteromultimeric fusion protein comprising a peptide linker that may vary from 1 to 500 amino acids, with 1 to 20 amino acids being preferred. One embodiment of Curtis et al. also teaches that the linker is preferably 11 amino acids or longer. Therefore, linkers taught by Curtis et al. vary widely in length. However, the combination of references fails to specifically teach or suggest joining EPO (or any other growth factor or cytokine) to an Ig domain using a linker that is between 2 and 7 amino acids and consists of glycine and serine, and moreover, the combination specifically suggests that the linkers should be longer than those claimed by the present invention. Therefore, the combination of references fails to teach each and every element of the present invention.

The Examiner contends that it would be obvious to use different forms of peptide linkers to join fusion proteins because linkers add flexibility. However, as discussed in detail in the Declaration of Dr. Cox, the literature teaches that the size and amino acid sequence of peptide linker can have a profound impact on the bioactivities of fusion proteins, and it is not obvious or correct that any linker could be used to create any fusion protein, simply because it might provide flexibility. Indeed, the literature teaches (discussed in the Declaration and below) that many linkers result in a biologically *inactive* protein, or in a protein with significantly reduced biological activity. Thus, without providing more specific peptide amino acid sequences and teaching that construction of biologically active fusion proteins can be made using such sequences (as is done in the present application), it is impossible to create any EPO-IgG fusion protein of a type envisioned by the WO 99/02709 reference and predict that the fusion protein will be biologically active (*i.e.,* the teachings of WO 99/02709 are insufficient to predictably produce an EPO-Ig domain fusion protein with biological activity without undue experimentation). The teachings of Curtis et al., which emphasize linkers of widely varying and mostly longer length than presently claimed, do not provide any further teaching with regard to the EPO-Ig fusions of WO 99/02709.

As discussed in the Declaration of Dr. Cox, the literature teaches that the size and sequence of peptide linkers can dramatically affect bioactivities of fusion proteins.

Moreover, much of the literature, including that cited by the Examiner, teaches that peptide linkers should be longer than the presently claimed linkers. For example, in the reference of Robinson et al. (see Declaration), only linkers with 13 or more amino acids resulted in biologically active proteins. Linkers with 3, 8 or 9 amino acids were inactive in the fusion of Robinson et al. and linkers with 11 amino acids were only partially active. Thus, the disclosure of Robinson et al. teaches away from using linkers of less than 11 or 13 amino acids for creating biologically active Epo/IgG fusion proteins. Also discussed in the Declaration, Qiu et al. (1998) reported that EPO-EPO fusion proteins joined by peptide linkers of 3-7 glycine residues have significantly reduced biological activities (4-10-fold) relative to wild type EPO, again teaching away from using linkers of this smaller size. As another example, Chang (U.S. Patent No. 5,723,125) describes alpha interferon/IgG-Fc fusion proteins joined by a peptide linker. Chang found that an alpha interferon fusion protein containing a 16 amino acid linker (GGSGGSGGGGSGGGGS) had 5-10-fold greater specific activity in anti-viral assays than a related alpha interferon/IgG-Fc fusion protein containing a smaller, 6 amino acid linker (GGSGGS) (see column 5, lines 43-50). Therefore, this reference teaches that the length of the linker can dramatically impact the biological activity of the resulting fusion protein, and further teaches that longer peptide linkers are preferred.

Therefore, Applicants submit that based on the literature, including the combination of references cited by the Examiner, one would find it unpredictable whether biologically active EPO/IgG fusion proteins could be constructed using the claimed linkers of between 2 and 7 amino acids that consist of glycine and serine. Indeed, one of skill in the art would be inclined to use linkers of a longer length, particularly given the literature that actually describes fusions with EPO, and certainly given the combination of references cited by the Examiner. However, in contradiction of such suggestions to use longer peptide linkers to create biologically active EPO fusions, the present inventors have *demonstrated* the use of linkers of 7 amino acids or less to produce biologically active EPO fusion proteins as presently claimed, thus providing a surprising result.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 2, 26, 42, 45, 46, 52, 53, and 62-65 under 35 U.S.C. § 103.

Rejection of Claims 2 and 3-5 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 2 and 3-5 under 35 U.S.C. § 103, contending that these claims are unpatentable over Sytkowski et al. (WO 99/02709) in view of Mapelli et al. Specifically, the Examiner references the previously discussed teachings of Sytkowski et al. Mapelli et al. is cited for allegedly teaching the construction of peptide linkers containing between 1 and 5 amino acids comprising serine and glycine. The Examiner asserts that it would have been obvious to modify the teachings of Sytkowski et al. using the peptide linkers of Mapelli et al. because linkers have been shown to provide flexibility to fusion proteins.

Applicants traverse the rejection of Claims 2 and 3-5 (now Claims 90, 93 and 94, respectively, noting that the subject matter of prior Claim 4 has been cancelled) under 35 U.S.C. § 103. Initially, Applicants refer to the discussion above regarding Sytkowski et al. and submit that the teachings of this reference are not sufficient to teach or suggest the fusion proteins having the peptide linkers recited in Claims 90, 93 and 94. With regard to Mapelli et al., this reference teaches the use of peptide linkers of 1 to 5 amino acids for the construction of a bridge between *oligopeptides*, which are relatively small monomer peptides that are linked together. However, reading further in column 25 at lines 29-41 of Mapelli et al., the patent teaches that secondary structures such as alpha helices or beta strands which are *undesired* in the oligopeptides of Mapelli et al. and which might hinder potential interactions between monomers generally require linkers of greater than 5 peptides. In contrast to the teachings of Mapelli et al., the claimed fusion proteins are not between oligopeptides that preferably have no secondary structures, but rather are between large proteins that *contain* alpha helices and beta strands. Therefore, not only are the claimed protein types clearly *not* the subject of Mapelli et al., Mapelli et al. clearly teach that for such proteins, larger peptide linkers are likely to be required. Therefore, the combination of WO

99/02709 and Mapelli et al. would not provide any further information with regard to the construction of EPO-Ig fusions than WO 99/02709 alone, and even if one considered the combination, at best, one would be motivated to use larger linkers in the fusion than are recited in the present claims. Finally, it is submitted that given that Mapelli et al. is directed to antimicrobial oligopeptides, there is no reason that one of skill in the art would look to this reference to provide any information about constructing fusion proteins between larger cytokine/growth factor proteins and immunoglobulins. In fact, Applicants submit that one of skill in the art would be dissuaded from using teachings regarding small oligopeptides to apply to the construction of large fusion proteins as claimed.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 2 and 3-5 under 35 U.S.C. § 103.

Rejection of Claims 22, 23, 58, 59 and 66 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 22, 23, 58, 59 and 66 under 35 U.S.C. § 103, contending that these claims are unpatentable over Sytkowski (U.S. Patent No. 6,242,570) in view of Mapelli et al. Specifically, the Examiner contends that the '570 patent teaches a linker including serine, glycine and asparagine that may vary without significantly affecting biological activity of the fusion protein. Mapelli et al. is cited for teaching linkers of from 1-5 amino acids comprising serine and glycine residues. Therefore, the Examiner contends that it would have been obvious to modify the teachings of the '570 patent to use the linkers of Mapelli et al.

Applicants traverse the rejection of Claims 22, 23, 58, 59 and 66 (now Claims 118 and 115, noting that prior Claims 23, 59 and 66 have been cancelled) under 35 U.S.C. § 103. Initially, Applicants refer to the discussion above with regard to the '570 patent and again submit that the only guidance provided with regard to the actual linker length for EPO-EPO fusions is that the EPO proteins should be separated by a linker length of 10-20 amino acids, although *longer* linker sequences may be used, with a preferred linker length of about 15 amino acids, and further, that the only multimeric fusion protein actually exemplified in the

'570 patent is an EPO-EPO dimer, joined by a peptide linker of 17 amino acids, and which contains alanine, glycine, serine and threonine amino acids. Indeed, the '570 patent appears to *teach away* from the use of the small linkers recited in the present claims. Therefore, the teachings of the '570 patent are outside of the presently claimed invention.

With regard to the combination of the '570 patent with Mapelli et al., for the reasons discussed above with respect to Mapelli et al., one of skill in the art would not combine Mapelli et al., which is directed to antimicrobial oligopeptides, with a reference disclosing fusion proteins between larger cytokine/growth factor proteins and immunoglobulins, particularly since Mapelli et al. state in col. 25 that secondary structures in their proteins are *undesirable*. In fact, Applicants submit that one of skill in the art would be dissuaded from using teachings regarding small oligopeptides to apply to the construction of large fusion proteins as claimed. Therefore, the Examiner has no basis to combine these references.

Moreover, *even if* one combines the references, also as discussed above, Mapelli et al. teaches that secondary structures such as alpha helices or beta strands which might hinder potential interactions between monomers generally require linkers of greater than 5 peptides. Therefore, the combination of the '570 patent and Mapelli et al. would not provide any further information with regard to the construction of EPO-Ig fusions than the '570 patent alone, and *even if* one considered the combination, at best, one would be motivated to use larger linkers in the fusion protein than are recited in the present claims, for the reasons discussed above.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 22, 23, 58, 59 and 66 under 35 U.S.C. § 103.

Rejection of Claims 60 and 61 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 60 and 61 under 35 U.S.C. § 103, contending that these claims are unpatentable over Amoresano et al. in view of Mapelli et al. Specifically, the Examiner contends that Amoresano et al. teach GM-CSF/EPO fusion protein and a peptide linker comprising glycine, serine and alanine residues. Mapelli et al. is cited for

teaching linkers of from 1-5 amino acids comprising serine and glycine residues. Therefore, the Examiner contends that it would have been obvious to modify the teachings of Amoresano et al. to use the linkers of Mapelli et al.

Applicants traverse the rejection of Claims 60 (now Claim 124) and 61 (now cancelled) under 35 U.S.C. § 103. With regard to Amoresano et al., as discussed previously in this response, Amoresano et al. teach an eight amino acid peptide linker comprising glycine, serine and alanine, and therefore, Amoresano does not teach the limitations of Claim 60. Moreover, for the reasons discussed in detail above with respect to combinations of other references with Mapelli et al., there is no reason that one of skill in the art would combine Mapelli et al., which is directed to antimicrobial oligopeptides, with a reference disclosing fusion proteins between larger cytokine/growth factor proteins and immunoglobulins. Furthermore, also for the reasons discussed in detail above with respect to combinations of other references with Mapelli et al., the combination of Amoresano et al. and Mapelli et al. would not provide any further information with regard to the construction of EPO-Ig fusions than Amoresano et al. alone, and even if one considered the combination, at best, one would be motivated to use larger linkers in the fusion protein than are recited in the present claims.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 60 and 61 under 35 U.S.C. § 103.

Rejection of Claims 32 and 33 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 32 and 33 under 35 U.S.C. § 103, contending that these claims are unpatentable over Sytkowski et al. (WO 99/02709) in view of Strom et al. (WO 99/02711). Specifically, the Examiner cites Sytkowski et al. for the reasons discussed above, and cites Strom et al. for teaching the cloning, expression and purification of human EPO fusion proteins that include column chromatography as a step. The Examiner contends that it would have been obvious to modify the teachings of Sytkowski et al. to use the

chromatography method of Strom et al.

Applicants traverse the rejection of Claims 32 and 33 (now Claims 85 and 86, respectively) under 35 U.S.C. § 103. Claim 85 recites a method to produce the fusion protein of Claim 67 (fusion protein without an intervening linker) and Claim 86 is a dependent claim therefrom. For the reasons discussed in detail previously herein and in the Declaration of Dr. Cox, WO 99/02709 fail to provide an enabling disclosure that teaches or suggests a fusion protein without an intervening linker, including an EPO-Ig fusion protein without an intervening linker. Therefore, and as also expressly discussed above, WO 99/02709 fails to teach or suggest any method by which such a protein could be produced. The deficiencies of this reference are not remedied by the teachings of Strom et al., as a teaching of expression and purification steps does not provide a teaching of the claimed fusion protein. Therefore, the combination of references fails to teach or suggest the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 32 and 33 under 35 U.S.C. § 103.

Rejection of Claims 38 and 44 Under 35 U.S.C. § 102 or § 103:

The Examiner has rejected Claims 38 and 44 under 35 U.S.C. § 102, or in the alternative, under 35 U.S.C. § 103, contending that these claims are anticipated by or unpatentable over Sytkowski et al. (WO 99/02709). The Examiner contends that Sytkowski et al. is silent with respect to the EC_{50} of the EP-Ig fusion protein. The Examiner further states that the Office does not have the facilities to compare Applicants' protein and the cited protein and therefore, in the absence of evidence to the contrary, the Examiner considers them to have no critical differences.

Applicants traverse the rejection of Claims 38 and 44 (now Claims 70 and 96, respectively) under 35 U.S.C. § 102 or 103. With regard to Claim 70, which recites an EPO-Ig fusion protein without an intervening linker, as discussed in detail previously herein and in the Declaration of Dr. Cox, WO 99/02709 fails to provide an enabling disclosure that teaches or suggests such a protein and therefore, fails to anticipate or make obvious the

claimed invention. Moreover, also for the reasons discussed previously herein and in the Declaration of Dr. Cox, with regard to Claim 96, which recites an EPO-Ig fusion protein with a peptide linker of between 2 and 7 amino acids consisting of glycine and serine, WO 99/02709 also fails to teach or suggest this protein, and therefore can not anticipate or make obvious the protein. Moreover, in view of the art discussed above which would teach away from making EPO fusions with short peptide linkers, the general knowledge in the art combined with WO 99/02709 also fails to teach or suggest the present invention as claimed.

Finally, the Examiner submits that the Office does not have the facilities to compare Applicants' protein and the cited protein. Applicants reply that as discussed in detail above, WO 99/02709 do not actually produce any EPO-IgG fusion protein and are completely non-enabling for the production of a fusion protein without an intervening linker. WO 99/02709 also do not provide sufficient information to produce an EPO-IgG fusion with a linker that will predictably have biological activity (also discussed above). Therefore, it is impossible to compare the protein of the present invention to a protein that does not exist or is not described in sufficient detail to be reliably produced.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 38 and 44 under 35 U.S.C. § 102 or 103.

Applicants have attempted to respond to all of the concerns set forth in the August 15 Office Action. Any additional questions or concerns should be directed to the undersigned agent at (303) 863-9700.

Respectfully submitted,

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